REMARKS

I. Status of the Claims

Claims 4, 6-8, 17, 20-28, and 47-48 are pending in the application following entry of this amendment. Claims 47 and 48 are new. Claims 4, 6, 17 and 20 have been amended. Claims 34 and 36-38 have been canceled without prejudice to pursuing the claims in a continuing application. Support for amendment to the claims can be found throughout the specification, and for example, on page 6, lines 2-4, and page 9, lines 28-30. Support for new claims 47 and 48 can be found throughout the specification, and for example, on page 10, lines 18-26.

Claims 4, 6-8, 17, 20-28, 34 and 36-38 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Maertens et al. (WO 96/13590, 9 May 1996) or Maertens et al. (US 2002/0183508 Al, December 5, 2002) or Selby et al. (*J. Gen. Virol.* **74**:1103-1113, 1993) or Donnelly et al. (WO 97/47358, 18 December, 1997) in view of Liao et al. (WO 96/38474), Tokushige et al. (*Hepatology* **24**:14-20, 1996) and Ferrari et al.(*Hepatology* **19**:286-295).

II. The claims are patentable under 35 U.S.C. § 103(a)

Claims 4, 6-8, 17, and 20-28 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Maertens et al. (Maertens et al. WO 96/13590, 9 May 1996) or Maertens et al. (Maertens et al. US 2002/0183508 Al, December 5, 2002) or Selby et al. (J. *Gen. Virol.* **74**:1103-1113, 1993) or Donnelly et al. (WO 97/47358, 18 December, 1997) in view of Liao et al. (WO 96/38474), Tokushige et al. (*Hepatology* **24**:14-20, 1996) and Ferrari et al. (*Hepatology* **19**:286-295). Applicants traverse the rejection.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation to modify the reference or to combine the reference teachings, there must be a reasonable expectation of success for achieving the claimed invention and its particular results, and the prior art must teach or suggest all the claim limitations. *See In re Vaeck*, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). For the reasons discussed below, a proper *prima facie* case of obviousness has not been set forth.

Independent claim 6 is directed to a recombinant nucleic acid molecule consisting of a nucleotide sequence encoding hepatitis C virus nonstructural proteins NS3, NS4 and NS5,

wherein said nucleotide sequence is operably linked to regulatory elements, said regulatory elements comprising a promoter, enhancer, polyadenylation sequence, and a 5' untranslated region (5'-UTR). Independent claim 17 is directed to a method of inducing an immune response against hepatitis C virus in a human uninfected by hepatitis C virus comprising administering to said human a recombinant nucleic acid molecule consisting of a nucleotide sequence encoding a hepatitis C virus nonstructural proteins NS3, NS4, and NS5, in an amount effective to induce an immune response against hepatitis C virus. The cited references fail to teach or suggest such a method or a recombinant nucleic acid molecule.

The examiner cited the Maertens et al. reference (WO 96/13590) and the Maertens et al. reference (US 2002/0183508 Al) as allegedly teaching a recombinant expression vector comprising a polynucleotide comprising sequences that express NS4, NS5 and also comprise 5'-UTR of hepatitis C virus. The Selby et al. reference allegedly teaches several constructs for expression of viral proteins, for example, plasmids pHCV5-1 and pHCV comprising the entire 5'UTR and 3'UTR and the coding sequence for the non-structural proteins. The Donnelly et al. reference allegedly teaches synthetic hepatitis C genes, pharmaceutical formulations and formulations for vaccination and gene therapy. The Donnelly et al. reference alleged teaches DNA constructs that encode hepatitis C NS5 gene or any other HCV gene that generates specific immune responses in animals. The Liao et al. reference allegedly teaches diagnosis of and vaccination against hepatitis C virus. The Liao et al. reference allegedly teaches that combining unprocessed non-structural protein (*e.g.*, NS5 protein or an unprocessed NS3-NS4 fusion protein) from HCV when combined with the unprocessed core region results in a synergistic effect of improved sensitivity and specificity.

The Tokushige et al. reference allegedly teaches a method of producing an immune response to hepatitis C virus core protein using a DNA based vaccine construct. Ferrari et al. allegedly teach a T cell response to structural and non-structural hepatitis C virus antigens in persistent and self-limited hepatitis C virus infections. The Ferrari et al. reference allegedly teaches that the core protein followed by the NS4 were the most potent T-cell immunogen for both chronic as well as asymptomatic anti-HCV-positive patients. Diepolder et al. allegedly teach a T cell response toNS3 and other nonstructural HCV proteins that contributes to successful viral clearance.

None of the references cited alone or in combination teach applicants' claimed invention, in part, a recombinant nucleic acid molecule consisting of a nucleotide sequence encoding hepatitis C virus NS3 protein NS4 protein NS5 protein, wherein the nucleotide sequence is operably linked to regulatory elements or a method of inducing an immune response against hepatitis C virus in a human uninfected by hepatitis C virus comprising administering to said human a recombinant nucleic acid molecule consisting of a nucleotide sequence encoding a hepatitis C virus nonstructural proteins NS3, NS4, and NS5. Furthermore, the examiner is impermissibly utilizing hindsight reconstruction to obtain applicants' claimed invention.

The examiner has not provided a motivation to combine the references to obtain applicants' claimed invention.

> "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

See MPEP 2143.01. The examiner states that the primary references, *e.g.*, Maertens et al.; Maertens et al.; and Donnelly et al., teach a recombinant expression vector expressing NS3 alone, NS5 alone or NS4 and NS5, alone or in combination with the HCV core protein. The Selby et al . reference teaches expression of the entire HCV viral genome. The examiner states that the secondary references, *e.g.*, Liao et al.; Tokushige et al.; Ferrari et al.; and Diepolder et al., teach methods of immunization with various combinations of NS3-NS4, or NS5, optionally in a mixture with core protein. The cited references do not teach or suggest the particular combination in a recombinant nucleic acid molecule encoding HCV nonstructural proteins NS3, NS4, and NS5. The cited references further do not teach or suggest the recombinant nucleic acid molecule wherein the nucleotide sequence encodes a fragment of at least 50 amino acids of NS3, NS4 or NS5, or the recombinant nucleic acid molecule with the specified promoter, enhancer, or 5'-UTR combinations, or a host cell comprising the recombinant nucleic acid molecule. Furthermore, the cited references do not teach or suggest a method of inducing an immune response against hepatitis C virus in a

human uninfected by hepatitis C virus comprising administering to said human a recombinant nucleic acid molecule consisting of a nucleotide sequence encoding hepatitis C virus nonstructural proteins NS3, NS4, and NS5, and the strong immune response generated by this combination when vaccinated into mice. The combination of references do not teach or suggest a strong humoral or cellular immune response generated by immunization with a recombinant nucleic acid molecule encoding HCV NS3, NS4, and NS5. The cited references further do not teach or suggest the method of immunizing with the recombinant nucleic acid molecule wherein the nucleotide sequence encodes a fragment of at least 50 amino acids of NS3, NS4 or NS5, or the recombinant nucleic acid molecule with the specified promoter, enhancer, or 5'-UTR combinations, or a pharmaceutical composition, optionally with a facilitator, bupivacaine, and comprising the recombinant nucleic acid molecule. One skilled in the art would not be motivated to combine the cited references to obtain applicants' claimed invention.

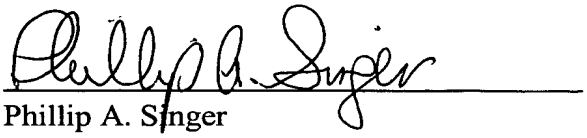
Accordingly, applicants respectfully request that the rejection of claims 4, 6-8, 17, and 20-28 under 35 U.S.C. § 103(a) be withdrawn.

VI. Conclusion

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

Date: November 9, 2004



Phillip A. Singer
Registration No. 40,176

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

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